1969

The desulphurisation of thionesters

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THE DESULPHURISATION OF THIONOESTERS

A Thesis submitted by

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SUMMARY

The mercury salt desulphurisations of the thiono esters were found to be dependent on the anion of the mercury salt, in a similar manner to the previously reported thioamide desulphurisations. Mercuric acetate reacts rapidly to give the corresponding ester and acetic anhydride. The reaction of mercuric chloride was much slower, giving a mixture of products. A mechanism is proposed for the mercuric acetate desulphurisation which predicts the formation of acetic anhydride. This mechanism is supported by the isolation of acetic anhydride in approximately the amount predicted. Desulphurisation of thiono esters with mercury carboxylates may be a useful synthesis of acid anhydrides.

I N T R O D U C T I O N

Use of Mercury Salts for Desulphurisation

Mercury (II) salts have been used for the desulphurisation of several types of organic sulphur compounds. Mercuric chloride converts hemithioketals to the corresponding ketones.[1] (fig. 1). Thioketals undergo a similar reaction with aqueous mercuric acetate[2] (fig. 2). A mixture of mercuric chloride and cadmium carbonate has been shown to have the same effect on thioketals.[3,4] (fig. 3).

Desulphurisation of Thiocarbonyl Compounds

The thiocarbonyl group also reacts with mercury salts. The products of the reactions of thioamides with mercury (II) salts are dependent upon the anion in the mercury salt. Petri and Lipiec[5] have shown that thioacetamide forms stable complexes with mercuric chloride which slowly hydrolyse to give mercuric sulphide. However, Taylor and Smith[6] report that mercuric acetate undergoes a very rapid reaction with thioacetamide in aqueous solution. Mercuric sulphide is precipitated at a rate much greater than can be explained by hydrolysis. They suggest a direct

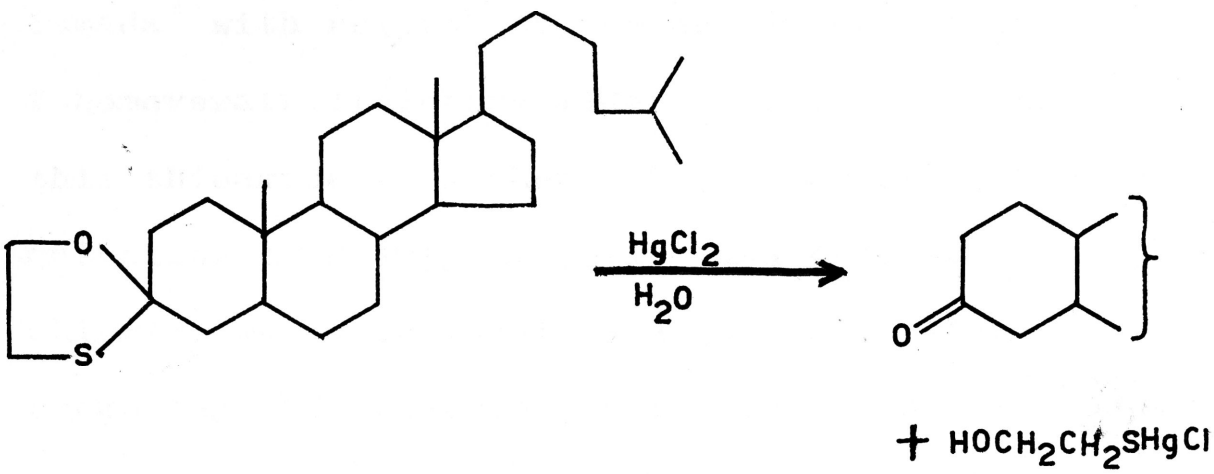


FIGURE 1

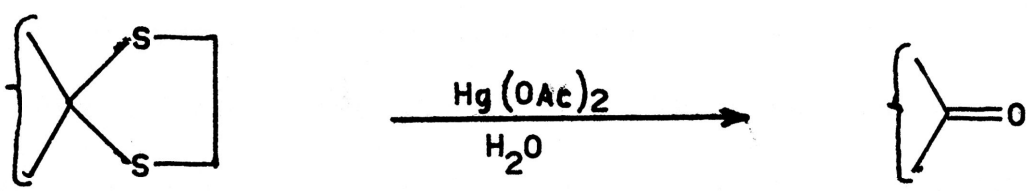


FIGURE 2

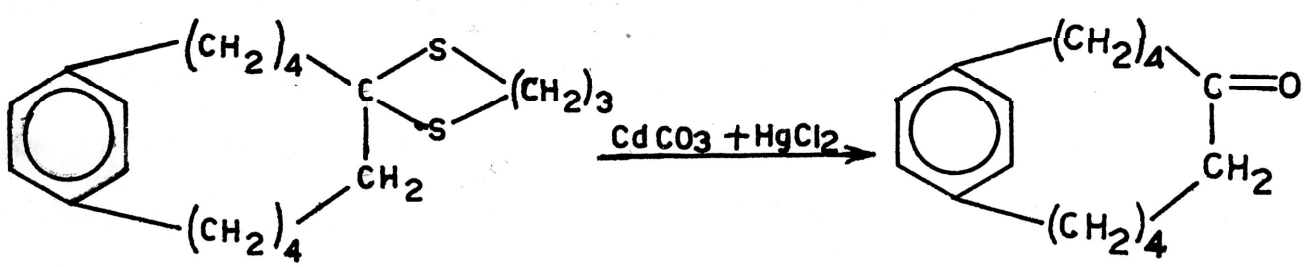


FIGURE 3

mechanism, not involving hydrolysis.

A similar effect is described by Hahsen, Omar and Yamada[7] with respect to the desulphurisation of N-homoveratrylthiobenzamide. They attempted to convert this thioamide to 1-phenyl-6,7.dimethoxy-3,4-dihydroisoquinoline by desulphurisation and cyclisation. Mercuric chloride was successful as a desulphurising agent in promoting this reaction, but mercuric acetate caused replacement of the sulphur by oxygen, without cyclisation (fig. 4.)

A further reaction of the thiocarbonyl group with mercury salts is the desulphurisation of trithiones by mercuric acetate[8] (fig. 5). This is similar to the mercuric acetate desulphurisations of thioamides in that the sulphur atom is simply replaced by oxygen.

Other desulphurising agents have been extensively used on thiol compounds and to a smaller extent on compounds containing the thiocarbonyl group. Raney nickel, in varying degrees of activation, has been successful in desulphurising a large number of compounds such as those reported by Latif and Choudbury[9] (fig. 6).

Raney nickel has also been used successfully for the preparation of olefins from thiocarbonates[10] (fig. 7). The initial reaction is cleavage of the C = S bond by

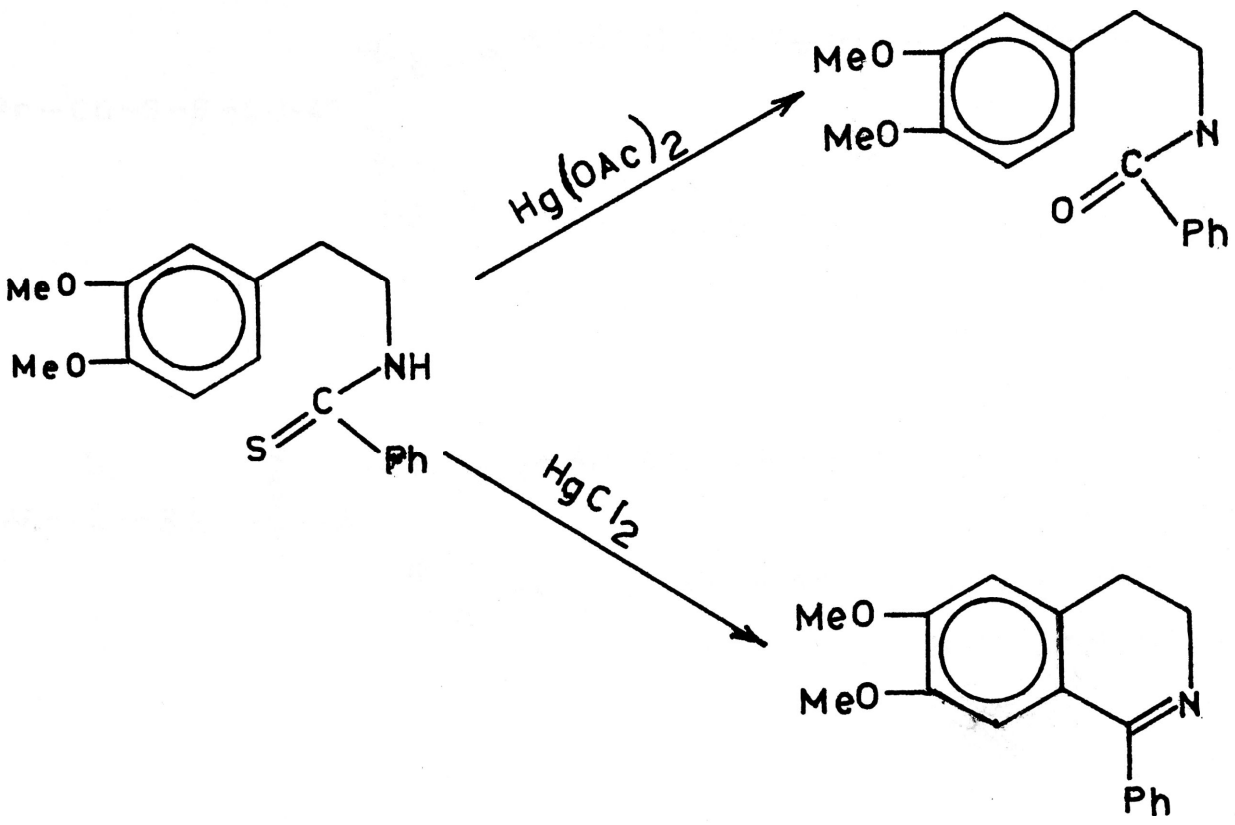
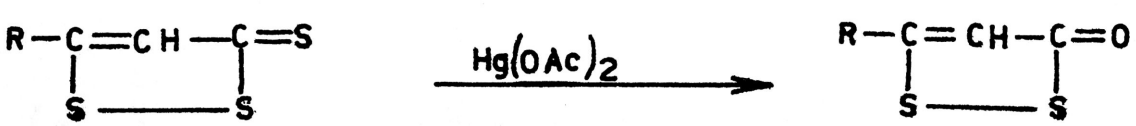


FIGURE 4



R = C_6H_5 or $C_6H_4OCH_3$

FIGURE 5

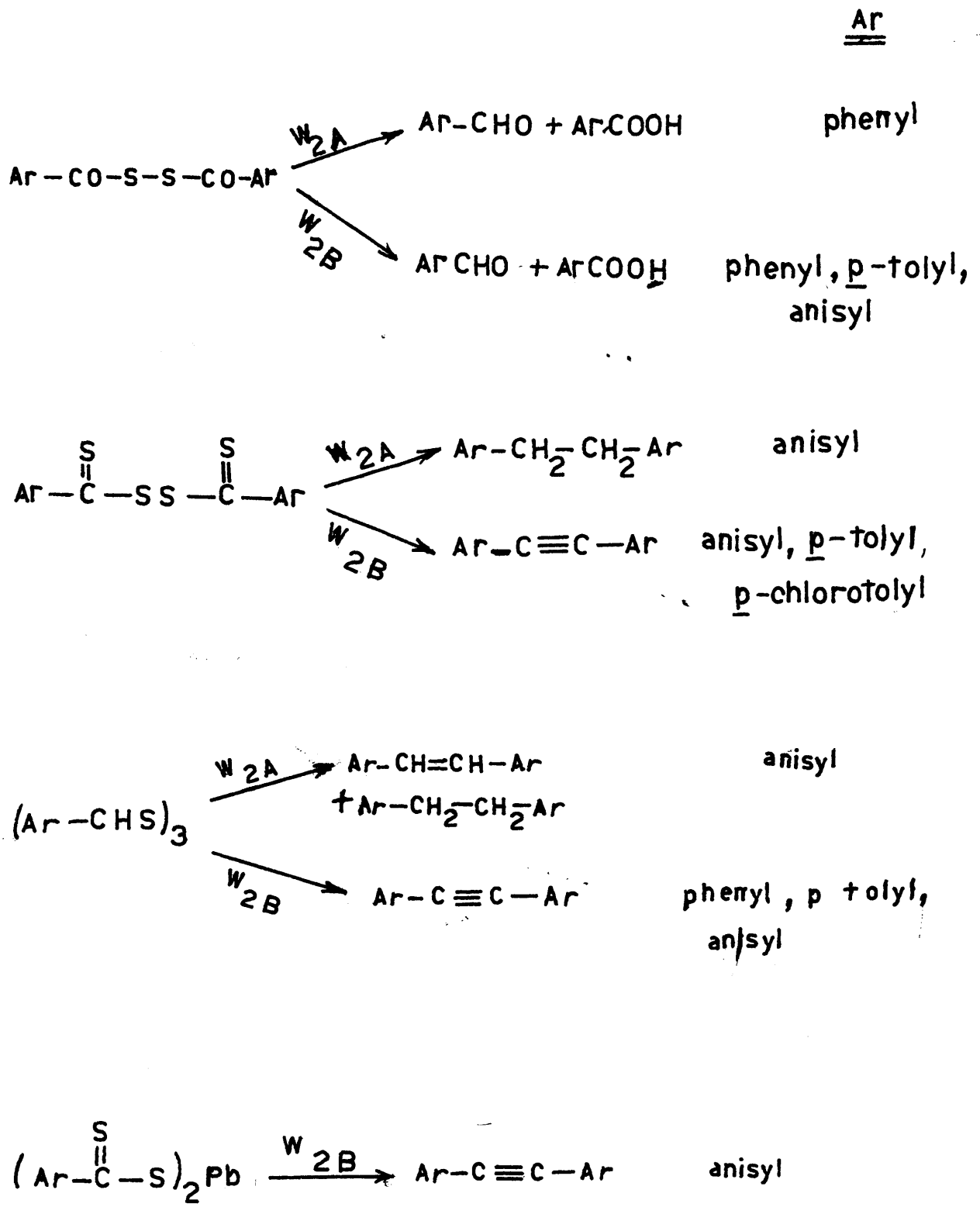

Ar
Ar-CO-S-S-CO-Ar
W2A
Ar-CHO + ArCOOH
phenyl
W2B
ArCHO + ArCOOH
phenyl, p-tolyl, anisyl
Ar-C(=S)-SS-C(=S)-Ar
W2A
Ar-CH2-CH2-Ar
anisyl
W2B
Ar-C≡C-Ar
anisyl, p-tolyl, p-chlorotolyl
(Ar-CHS)3
W2A
Ar-CH=CH-Ar
+Ar-CH2-CH2-Ar
anisyl
W2B
Ar-C≡C-Ar
phenyl, p tolyl, anisyl
(Ar-C(=S)-S)2Pb
W2B
Ar-C≡C-Ar
anisyl
SOLVENT
W2A ETHANOL
W2B ANHYDROUS BENZENE

FIGURE 6

Raney nickel, triethylphosphite or trimethylphosphite, followed by expulsion of CO_2.

Thiamides are susceptible to Raney nickel desulphurisation, the sulphur being replaced by 2 hydrogen atoms. Cronyn and Goodrich[11] have done some research in this field and the results of a number of investigations have been reviewed by Pettit and Tamelen[12]. Figure 8 shows the general scheme of these reactions.

The photolysis method for desulphurisation has not been extensively studied but data is available for thiocarbamates and thionoesters. Dimethylthiocarbamates of sugars are converted to the corresponding deoxy-sugars by irradiation by a mercury-arc lamp for 200 hours.[12] Figure 9 shows one of the types of sugars that have been investigated.

Ethyl thionoacetate is the only thionoester for which desulphurisation data has been published. Schmidt and Kabitzka[13] irradiated ethyl thionoacetate with UV light with wavelength 254 mμ. Fission of the C = S bond occurred, followed by combination of 2 molecules, forming a new C = C bond. The final product is as shown in figure 10.

This reaction prompted the present investigation of the desulphurisation of thionoesters. Particular

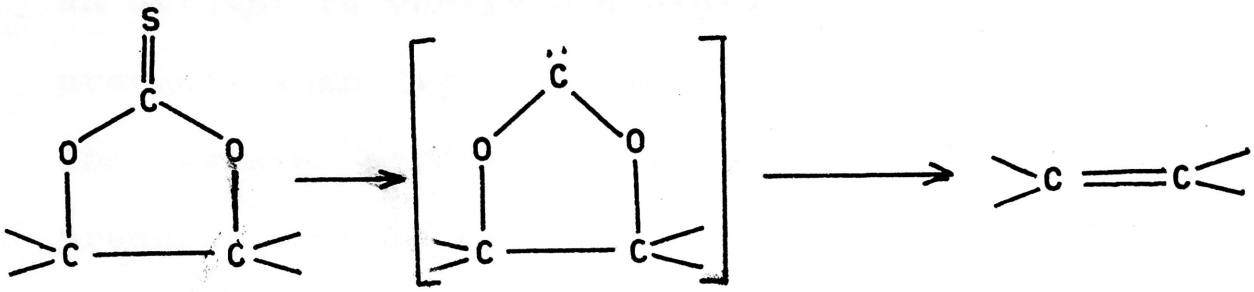


FIGURE 7

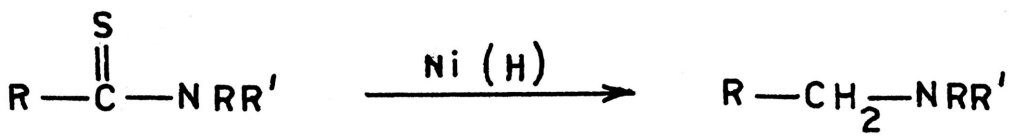


FIGURE 8

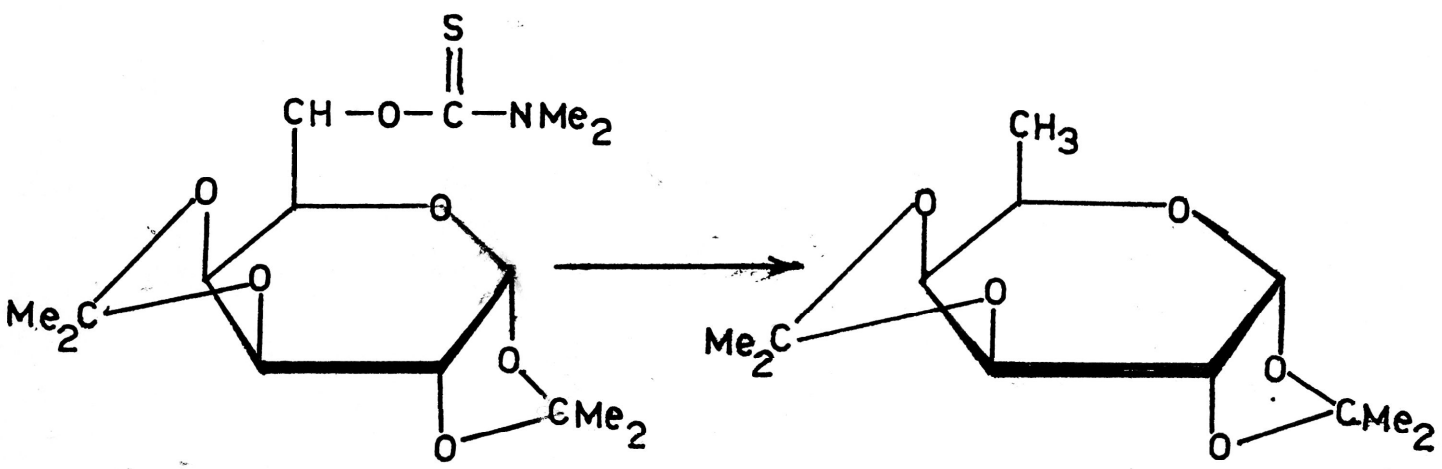


FIGURE 9

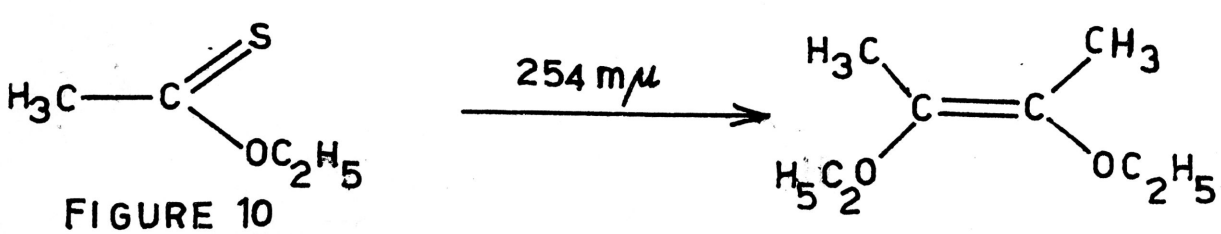


FIGURE 10

attention was given to the use of mercury salts, in an attempt to verify and explain the variation in products when different mercury (II) salts are used. The striking effect of the mercury salt anion on the products from thioamides suggests two distinct desulphurisation mechanisms.

D I S C U S S I O N

Synthesis of Thionoesters

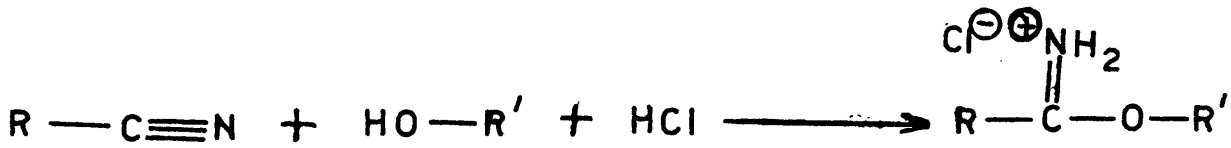
The Pinner synthesis of thionoesters begins with the condensation of an alcohol with a nitrile in the presence of hydrogen chloride to form an iminoester hydrochloride. In this synthesis, described by Matsui[14] and used for most syntheses until 1962, the iminoester hydrochloride is converted to the free iminoester by shaking the iminoester hydrochloride with an aqueous basic solution. The chloroform solution of the free iminoester is saturated with dry hydrogen sulphide to convert the iminoester to a thiono ester. The preparation is shown in figure 11a.

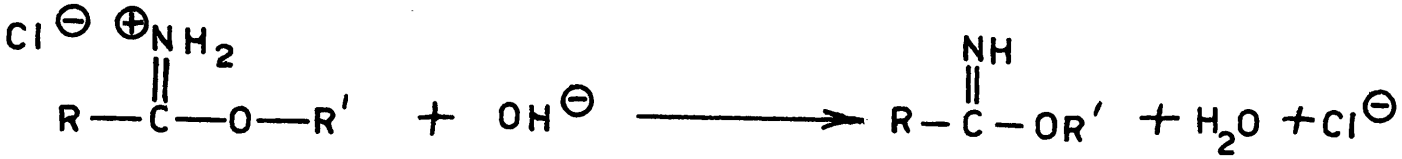
There are several disadvantages with this preparation:

(1) The free iminoester is unstable and difficult to work with.

(2) In some cases thioamides constitute a significant fraction of the products. Reynaud and Moreau[15] have proposed a mechanism for this side reaction (fig. 11b).

Schmidt, Heymann and Kabitzke[16] solved these problems by using pyridine as the solvent for the second step of the preparation. The iminoester hydrochloride is isolated as such and not as the unstable free iminoester.





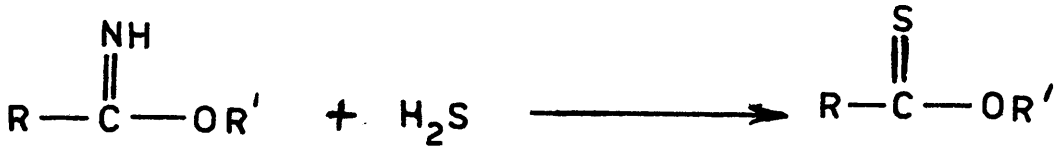
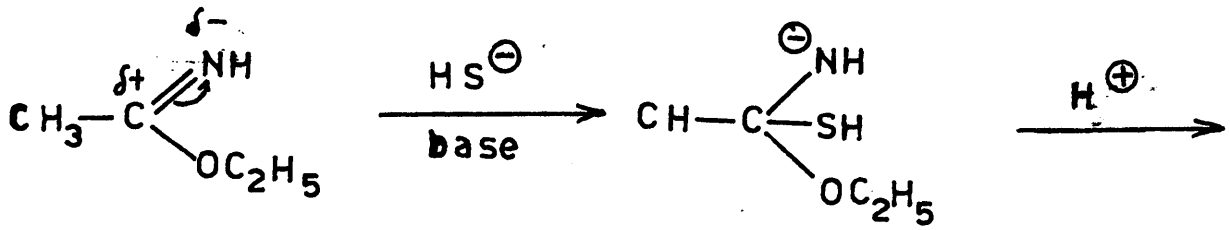


FIGURE 11a



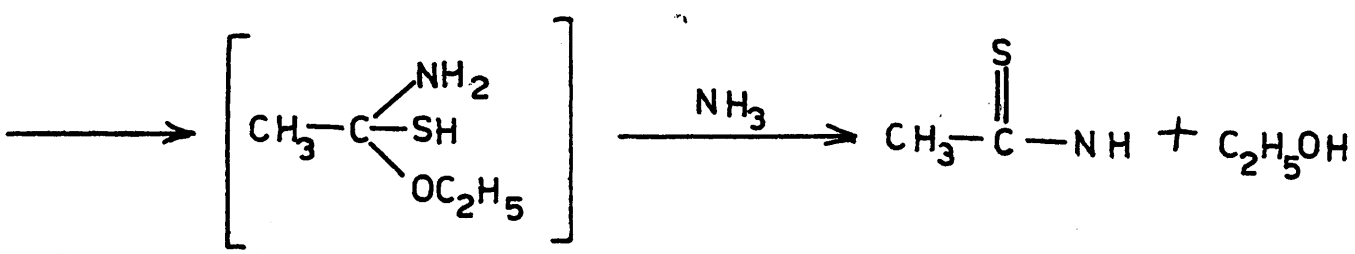


FIGURE 11b

The yield of thionoesters from this improved synthesis are very good, with less side products such as thioamides. This method is shown in figure 12. The thionoesters used in the present work were prepared by this method. The yields were as follows:

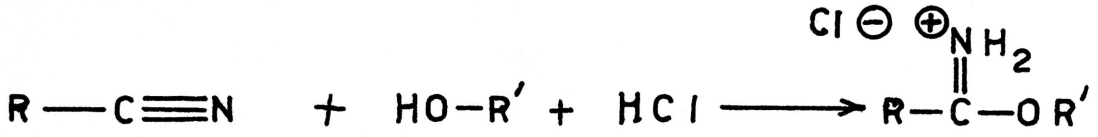
Cholestanol Thionoacetate	81%
Cyclohexyl Thionoacetate	77%

Attempted Preparation of Benzhydrol Thionoacetate

The main product of this preparation was a white solid which had a melting point of 107-108°C. The IR spectrum did not contain the pair of very strong bonds at 1180-1190 and 1265-1285 cm^{-1} which are characteristic of thiono esters.[15] The spectrum in the region 800-4000 cm^{-1} showed strong bonds at 1000-1100 cm^{-1}, 1550 cm^{-1} and 3020-3050 cm^{-1} with weaker bonds at 1200-1300 cm^{-1}. The broad bond at 1000-1100 cm^{-1} could be attributed to C - O stretching in an ether.

The NMR spectrum consisted of a multiplet at τ 2.7 and a singlet at τ 4.6. The integrated peak areas of these signals were in the ratio of 10:1.

A signal at τ1.5-4 is characteristic of aromatic hydrogen atoms, and a signal at τ4-5 could be due to a



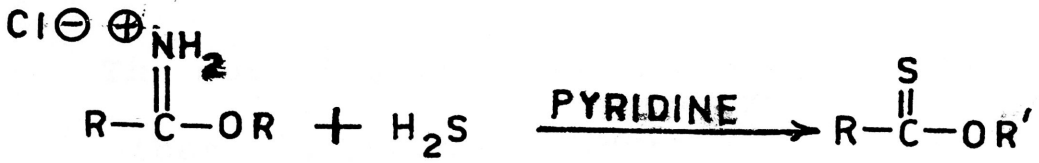


FIGURE 12

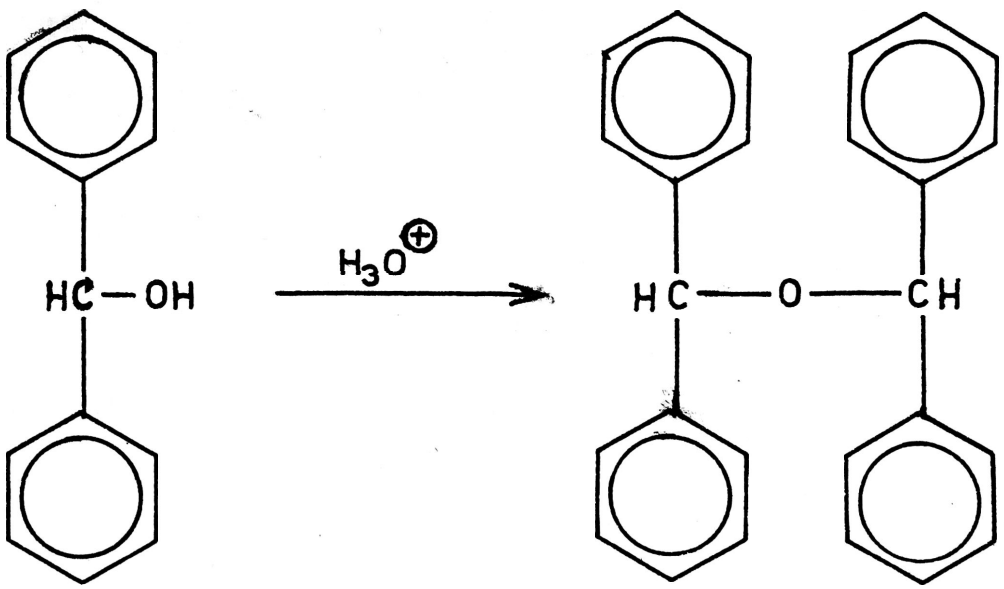
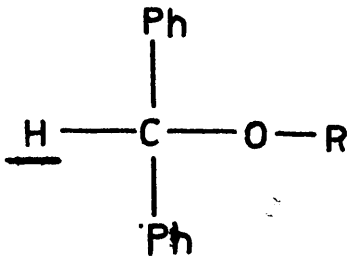


FIGURE 13

hydrogen atom of the type



The most likely structure of this compound is dibenzhydrol ether, as shown in figure 13, lit. 17 MP = 109-110°. This compares favourably with the measured melting point of 107-108°. Balfe, Doughty, Kenyon and Poplett[18] have shown that *p*-methoxybenzhydrol and its esters readily undergo alkyl-oxygen cleavage in aqueous acidic solution to form *p*-methoxybenzhydryl ether. The lability of this bond is attributed to the stability of the *p*-methoxybenzhydryl cation due to the electron donating effect of the aromatic rings.

DESULPHURISATION OF CHOLESTANOL THIONOACETATE

TABLE 1 - SUMMARY OF RESULTS

Desulphurising Agent	Solvent	Rate of Reaction	Colour of Precipitate	Products	Yield %	Identification
Raney Nickel	Benzene	-	-	Cholest-2-ene	19.3	TLC, MP
				Cholestanol acetate	28.9	TLC, MP, IR
				Cholestanol	43.9	TLC, MP
				Cholestanol thionoacetate	2.3	TLC, MP
Mercuric Acetate	Acetic Acid	Fast	Black	Cholestanol acetate	88.8	TLC, MP
Mercuric Acetate	Propionic Acid	Fast	Black	Cholestanol acetate	90.3	TLC, NMR
Mercuric Acetate	Pyridine	Fast	Black	Cholestanol acetate	89.0	TLC
				Cholestanol	3.4	TLC
Mercuric Chloride	Acetic Acid	Slow	White	Cholestanol acetate	89.3	TLC
Mercuric Chloride	Propionic Acid	Slow	White	Cholestanol acetate	95.8	TLC, MP
Mercuric Chloride	Ethanol	Slow	Yellow	Cholestanol acetate	93.7	TLC
Mercuric Chloride	Ether	Slow	White	Cholestanol acetate	84.8	TLC
				Cholestanol thionoacetate	8.5	TLC
Mercuric Chloride	Pyridine	V.Slow	Yellow	Cholest-2-ene	7.9	TLC
				Cholestanol thionoacetate	5.3	TLC
				Cholestanol acetate	68.4	TLC, MP
				Cholestanol	13.7	TLC
Mercuric Chloride in sealed ampule at 100°C for 20 hours	Pyridine	V.Slow	White changing to red	Cholest-2-ene	21.0	TLC
				Cholestanol thionoacetate	13.2	TLC
				Cholestanol acetate	67.0	TLC
Mercury Benzamide	Acetic Acid	Fast	Black	Cholestanol acetate	94.2	TLC, MP
Mercury Benzamide	Pyridine	No visible reaction				

KEY TO IDENTIFICATION METHODS:

TLC	-	Thin layer chromatography
MP	-	Mixed melting point with authentic specimen
IR	-	Infra-red spectroscopy
NMR	-	Nuclear magnetic resonance spectroscopy

Raney Nickel Desulphurisation

The products are as shown in Table 1. A free radical mechanism, as suggested by Djarassi[1] for the desulphurisation of hemithioketals, is most likely. The Raney nickel reacts with the sulphur atom of the cholestanol thionoacetate forming nickel sulphide. The large amount of cholest-2-ene compared with cholestane indicates that the Raney nickel was almost completely deactivated, since an activated catalyst would cause considerable hydrogenation of the unsaturated cholest-2-ene. A freshly prepared sample of Raney nickel would probably give a different proportion of each product.

Desulphurisation with Mercury Salts

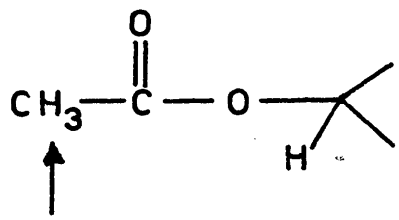
(a) Mercuric Acetate in Acetic Acid Solvent

A granular black precipitate was formed immediately upon adding the mercuric acetate. Acetoxycholestane was the only product. Figure 14 illustrates the two mechanisms by which the sulphur atom could be replaced by oxygen. In mechanism (1) only the sulphur atom is removed, to be replaced by an oxygen atom. In Mechanism (11), alkyl-oxygen cleavage occurs, followed by condensation between the hydrocarbon fragment and an acetoxy group from the solvent or from the mercuric acetate.

FIGURE 14

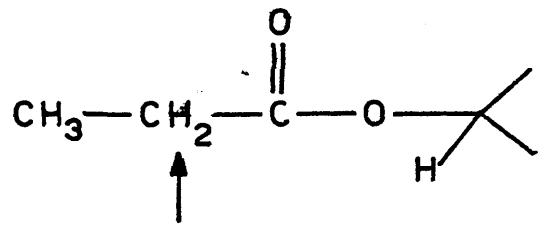
MECHANISM (I)

CHOLESTANOL ACETATE



MECHANISM (II)

CHOLESTANOL PROPIONATE



NMR SIGNALS

3H SINGLET AT $\tau = 8{\cdot}0$

2H QUADRUPLET AT $\tau = 7{\cdot}7$

FIGURE 15

If mechanism (1) is correct, desulphurisation of cholestanol thionoacetate using any carboxylic acid as solvent should produce cholestanol acetate as the only product. If mechanism (11) is correct, the use of propionic acid as solvent should cause cholestanyl propionate to be the major product since the propionate ion concentration in solution would be much larger than the acetate ion concentration. Figure 15 shows the expected products for each mechanism and their most prominent NMR signals.

(b) Desulphurisation with Mercuric Acetate in Propionic Acid Solvent

Only one product was formed, having an NMR spectrum containing a 3 proton singlet at τ = 8.0.

This strongly supports mechanism (1) which involves cleavage of the C = S bond. However, the source of the oxygen is still uncertain. It could be derived from either the solvent or the mercuric acetate. To determine whether the mercuric acetate alone is a sufficient source of oxygen to sustain the very rapid reaction, a desulphurisation was carried out using mercuric acetate in pyridine. The reaction once again was extremely rapid with complete conversion of the cholestanol thionoacetate to cholestanol acetate. A black precipitate was formed as before. Therefore, the mercuric acetate is capable

of supplying all the oxygen required to desulphurise the thionoester. However this does not exclude the possibility that the oxygen could be derived from the solvent.

Desulphurisation with Mercuric Chloride

Mercuric chloride when added to a solution of cholestanol thionoacetate in acetic or propionic acid caused a slow reaction. A granular white precipitate was formed over a period of several minutes. The cholestanol thionoacetate was almost completely converted to cholestanol acetate after ten minutes. This shows that the solvent is not a sufficient source of oxygen to sustain the fast reaction observed with mercuric acetate.

Mercuric chloride desulphurisations in dry ethanol and sodium dried ether similarly gave slow conversion of the cholestanol thionoacetate to cholestanol acetate, accompanied by the formation of a white or pale yellow precipitate. The oxygen required for this reaction may be derived from the solvent. When the mercuric chloride desulphurisation was repeated in pyridine the reaction was slower, being incomplete after 30 minutes. The appearance of cholest-2-ene as a product suggests that a disproportionation of oxygen from the thiono ester is taking place. If this is true, cholestanol acetate and

cholest-2-ene should be formed in equal molar amounts. The excess of cholestanol acetate may be due to atmospheric oxidation of the thionoester. To eliminate this atmospheric oxygen, the desulphurisation was repeated in a sealed ampule which had been swept with dry nitrogen. The proportion of cholest-2-ene in the products rose but still did not equal the cholestanol acetate. The source of the excess oxygen in the products could be atmospheric oxygen dissolved in the solvent. Alternatively, oxidation of unchanged cholestanol thionoacetate could be taking place during separation of the products on the silica gel chromatography column.

Mercury Benzamide Desulphurisation

When mercury benzamide was used as a desulphurising agent in acetic acid solvent the reaction was similar to that of mercuric acetate. A black precipitate was immediately formed, along with cholestanol acetate in almost quantitative yield. However when pyridine was used as solvent, no visible reaction occurred, even after prolonged heating. The inference is that the acetate group is necessary for the fast reaction. The fast reaction of mercury benzamide in acetic acid is probably due to partial or complete anion exchange between the mercury salt and the solvent. Although the small ionisation constant of mercuric acetate might be expected

to prevent fast exchange, the acidity of acetic acid which is much greater than that of benzamide assists rapid exchange. Addition of a small amount of acetic acid to the reaction mixture with pyridine as solvent caused an immediate reaction similar to that of mercuric acetate.

Proposed Mechanism of Mercuric Acetate Desulphurisation

The desulphurisations with mercuric chloride and mercury benzamide indicate that the rapid reaction with mercuric acetate is due to a reaction of the mercuric acetate as a whole, and not of the mercuric ion alone. The acetate group must play an important part in the reaction mechanism.

The rate of the mercuric acetate desulphurisation is abnormally fast for an organic reaction. Such a rate would be favoured by a very stable transition state such as the sterically favourable six-membered ring.

The proposed reaction mechanism involves 2 transition states containing six-membered heterocyclic rings. Figure 16 illustrates how the reaction is initiated by electrostatic attraction between electron excessive sulphur atom and the partially ionised mercury atom. The carbonyl oxygen of one of the acetate groups can

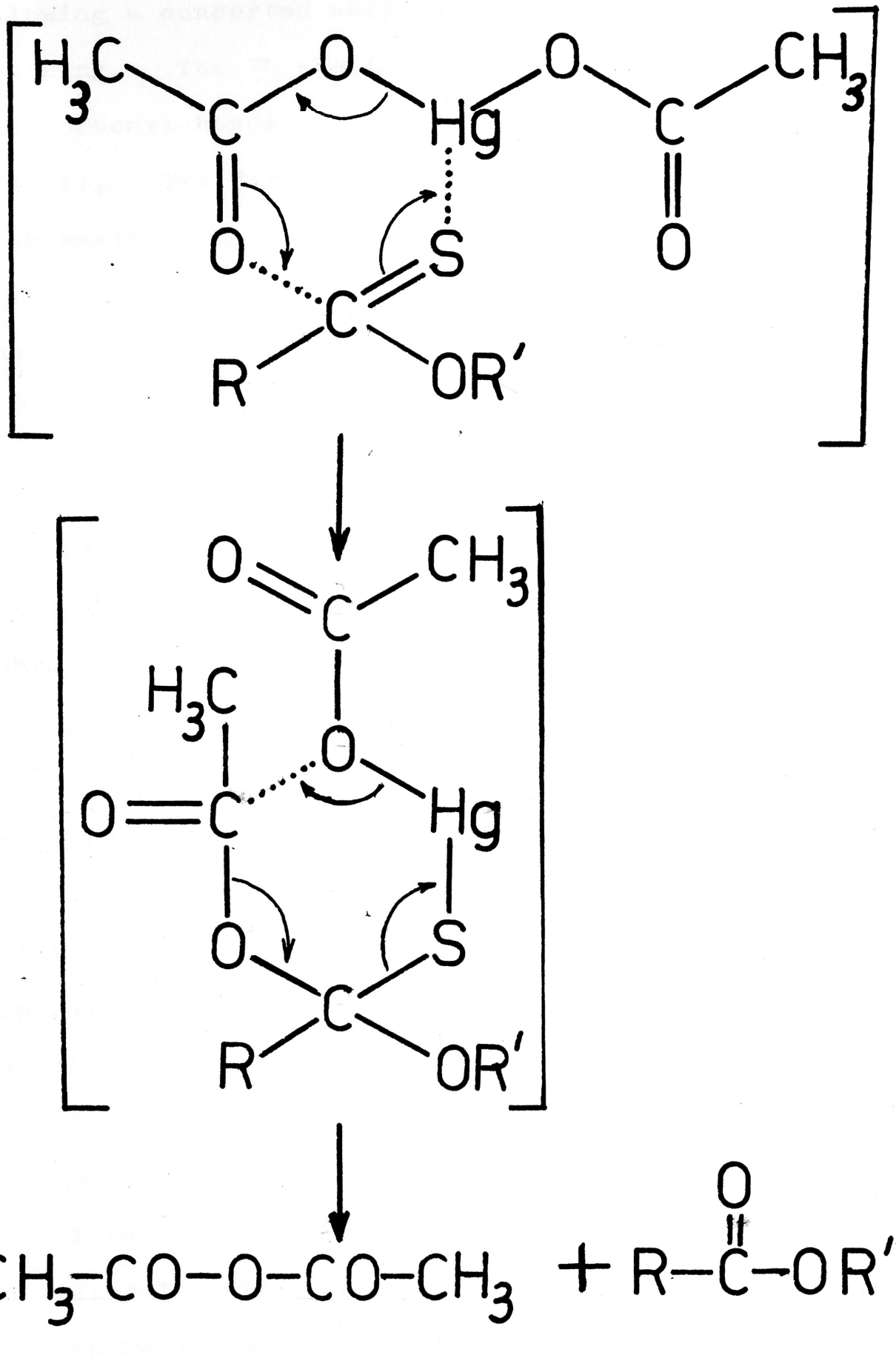

H3C
O
O
CH3
C
Hg
C
O
O
S
C
R
OR′
O
CH3
C
H3C
O
O
C
Hg
O
S
C
R
OR′
CH3–CO–O–CO–CH3
+ R–C(=O)–OR′
+ HgS

FIGURE 16

freely approach the carbon atom of the thiono ester, allowing a concerted shift of 3 pairs of electrons around the ring. The π electrons of the carbonyl and thiocarbonyl bonds are sufficiently free to allow such a shift, The first transition state rearranges to form another six-membered ring with little steric strain. A second concerted shift of 3 pairs of electrons around the ring completes the reaction.

The most important consequence of this mechanism is that acetic anhydride is predicted to be a product. The molar ratio of acetic anhydride to ester in the products should be one to one. Detection of acetic anhydride in the product mixture would be strong evidence to support this mechanism.

Mercuric Acetate Desulphurisation of Cyclohexyl Acetate

Acetic anhydride is too volatile to be isolated by column chromatography, which was the method used for separation of the products of all the previous reactions. Gas chromatography is more suitable for the separation of volatile materials and has the added advantage that the amount of each compound in the mixture can be calculated from the area of the recorder peaks. Because cholestanol acetate is not sufficient volatile to allow its separation by this method, cyclohexyl thionoacetate was used for the subsequent desulphurisations.

A silicone column was chosen as being most suitable since it gave the best separation of the products within a reasonable retention time. Pyridine proved to be unsuitable as a solvent since it gave a massive peak on the recorder chart which obscured the acetic anhydride peak. After investigation of a number of pyridine derivatives, γ-picoline was chosen. The peak due to γ-picoline was mid-way between the acetic anhydride and cyclohexyl acetate peaks and obscured neither of these.

The desulphurisation of cyclohexylacetate by mercuric acetate was carried out and the organic products were separated from the mercuric sulphide as described in the experimental section. 5 μl of the organic product mixture was injected into the gas chromatograph. Calibration graphs had previously drawn up which allowed the molar ratio of acetic anhydride to cyclohexyl acetate in the mixture to be calculated from the relative areas of their respective peaks on the recorder chart. The molar ratios of cyclohexyl acetate to acetic anhydride for two independent desulphurisations were found to be:

1) 1.15:1 2) 1.10:1

Loss of acetic anhydride by hydrolysis and incomplete distillation from the mercuric sulphide would be sufficient to explain the 10-15% deviation from the

expected 1:1 ratio of products.

Dimethylaniline was used as an internal standard to determine the yield of each product. The yields from 20 mg of cyclohexyl thionoacetate were found to be:

cyclohexyl acetate	82.1%
acetic anhydride	74.7%

The total recovery of organic material was 79.0%.

The detection of acetic anhydride as a reaction product with a yield close to that predicted by the proposed mechanism provides strong evidence that the proposed mechanism is correct.

Mercury Benzamide Desulphurisation of Cyclohexyl Thionoacetate

In pyridine solution no precipitate was formed, but after 30 minutes the solution was shown, by thin-layer chromatography, to contain cyclohexyl acetate and benzamide as well as unchanged cyclohexyl thionoacetate. This reaction is possibly due to aerial oxidation of the cyclohexyl thionoacetate.

Analysis of Precipitate from Mercuric Chloride Desulphurisations

The white or pale yellow precipitate formed during mercuric chloride desulphurisations was analysed for mercury, sulphur and chloride. The precipitate from

ethanol was a stronger yellow colour originally, but this precipitate and that from acetic acid solution both turned yellow after a few hours. There were no significant differences in the analyses of the precipitates from different solvents. The % mercury in the precipitate was found to be 70.6 ± 0.4%. The % S was found to be 8.5 ± 0.6%.

The total recovery of sulphur from one particular desulphurisation was found to be 80.3%.

The chloride could not be determined accurately. The results of a large number of analyses showed a very large random error. The Mohr and Volhard volumetric method and a gravimetric method all failed to give consistent results. Tests with pure mercurous chloride indicated that this was due to the method of bringing the chloride into solution before analysis. Boiling aqueous sodium carbonate solution failed to bring all of the chloride from pure mercurous chloride into solution. A recovery of 75-80% of the chloride was obtained. The alternative method of fusion with a sodium carbonate/potassium carbonate mixture caused some loss of mercurous chloride by volatilisation.

As qualitative tests indicated that the precipitate contained mercury primarily in the +1 oxidation state,

an attempt was made to determine the amount of mercurous chloride by a redox titration. The results obtained varied with the method of drying the precipitate and also with the time elapsed between formation of the precipitate and the analysis. The precipitate appears to be undergoing an oxidation/reduction reaction in the solid state, possibly by absorption of atmospheric oxygen. The colour change of the precipitate after drying supports this explanation.

When the precipitate was washed with carbon disulphide a weight loss occurred suggesting that the sulphur is present as elemental sulphur. On repeated washing, the weight loss continued beyond 12%, although the weight loss after each washing was much less than for the first three washings. This may be due to the non-sulphurous part of the precipitate also being slightly soluble in the carbon disulphide. Analysis of the residue by the redox titration method indicated that this was 98% mercurous chloride. In view of the earlier difficulties with this method this figure may have no real significance.

Synthetic Application of the Mercuric Acetate Desulphurisation

The reaction of carboxylic acid salts of mercury with a thionoester may offer to be a useful method for the synthesis of anhydrides. The proposed mechanism

for the reaction is such that any carboxylic acid salt of mercury should react in the same manner. Substituents on the methyl group of the acetate parts of the mercuric acetate are sufficiently remote from the reaction centre to cause very little steric hindrance to the attainment of the transition states.

The synthesis would be rapid and efficient. The mercury salt would be formed by heating the appropriate carboxylic acid with mercuric oxide or by mixing equivalent amounts of mercuric nitrate solution and sodium carboxylate.

Any unconverted acid could be recovered easily and re-used. The mercury salt would then be dissolved in a suitable solvent and added to a solution of any thiono ester. The acid anhydride would be expected to form immediately in near-quantitative yield. The volatile components could be separated from the mercuric sulphide by distillation or filtration and the anhydride isolated by preparative gas chromatography or fractional distillation. This synthesis may prove more efficient and convenient than the present methods[19] which are summarised below:

(1) The reaction of the acid chloride with the corresponding dry sodium salt. The preparation of the acid chloride and the drying of the sodium carboxylate require considerable time.

(2) By the reaction of ketene with acids. A supply of ketene must be maintained. This is prepared by the pyrolysis of acetone, requiring a considerable amount of equipment.

(3) By the reaction of the acid chloride with the acid in pyridine. Again the preparation of the acid chloride takes a considerable time.

E X P E R I M E N T A L

All melting points were determined in glass capillaries and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer model 237 recording spectrophotometer in carbon tetrachloride solution, except for the precipitate from the mercuric chloride desulphurisations which was in the form of a Nujol mull.

Ultraviolet-visible spectra were recorded on a Perkin-Elmer model 137 recording spectrophotometer in ethanol solution.

Optical rotations were measured in a 10 cm tube, using chloroform as solvent.

All gas chromatography was done on a Carle model 8000 gas chromatograph with a TOA Electronic Polyrecorder model EPR-2TB.

Analyses are by the Australian Microanalytical Service, Melbourne.

Nuclear magnetic resonance spectra were recorded on a Varian A60 spectrometer using deuterochloroform as solvent and tetramethylsilane as internal reference.

The petroleum ether used for column chromatography had b.p. 40-60°.

Benzene was dried over anhydrous magnesium sulphate and stored over sodium.

Super-dry ethanol was prepared by the method of Vogel[21].

Ether was dried and stored over sodium.

Hydrogen chloride was prepared by dropping concentrated hydrochloric acid into concentrated sulphuric acid with stirring. The gas was dried by bubbling through concentrated sulphuric acid.

Hydrogen sulphide was prepared in a Kipp's generator. Acid spray was removed by bubbling through water, followed by a calcium chloride tower to dry the gas.

Propionic acid was purified by distillation.

Pyridine and γ-picoline were dried by distillation and were stored over potassium hydroxide.

Thin Layer Chromatography

Thin layer chromatography plates were prepared by immersing 2" x 1" glass plates in a suspension of silica gel in chloroform. Steady and continuous

withdrawal of the plates from the suspension was necessary to ensure an even coating of silica gel. The plates were developed by sulphuric acid charring for high boiling point materials (cholestanol derivatives), and by iodine vapour absorption for volatile materials (cyclohexanol derivatives). Spots were identified by mixed Rf with authentic compounds.

Column Chromatography

All mixtures except those containing thionoesters were separated on neutral alumina columns using a 30:1 alumina : solute ratio. Mixtures containing thionoesters were separated on silica gel columns since alumina causes oxidation of thionoesters. An alumina : solute ratio of 100:1 was used. Constituents of the fractions collected were identified by thin layer chromatography. Solvents were removed from these fractions by distillation under vacuum in a Buchi rotary evaporator.

Attempted Synthesis of Benzhydrol Thionoacetate

Benzhydrol (5.0 g) was dissolved in chloroform (50 ml) and acetonitrile (30 ml). Dry hydrogen chloride was passed for two hours through the solution which was cooled in an ice bath. After standing for two hours in a refrigerator, the solution was evaporated down under vacuum. The residue was dissolved in pyridine,

then cooled in ice and hydrogen sulphide was passed for four hours. Chloroform (50 ml) was added and the pyridine was extracted into dilute hydrochloric acid solution. After washing with distilled water the chloroform solution was evaporated down. The residue was chromatographed on silica gel (300 g). The main product was shown to be dibenzhydryl ether, m.p. (after recrystallisation from chloroform/methanol) 107-108°. (Lit[17] 109-110°).

Synthesis of Cholestanol

Cholesterol (20.0 g), suspended in ethyl acetate (60 ml), was added to pre-reduced Adams catalyst (0.8 g) in ethyl acetate (500 ml). After addition of a few drops of perchloric acid, the suspension was hydrogenated for one hour. The catalyst was filtered off and the product was washed through with chloroform. The solvent was removed by distillation under vacuum and the residue refluxed with ethanolic sodium hydroxide (200 ml) for one hour. The solution was poured into water, acidified, and the cholestanol extracted into chloroform. The 5α-cholestanol was separated from the 5β-isomer by recrystalisation seven times from chloroform/methanol. The purity of the product was checked by MP and optical rotation:

MP = 139-141°, $(\alpha)_D$ = 24.4° (1% solution in chloroform)
(Lit[20] MP 140.5°, Lit[20] $(\alpha)_D$ 27.4°)

Synthesis of Cholestanol Thionoacetate

Cholestanol (5.0 g) was dissolved in a mixture of chloroform (50 ml) and acetonitrile (30 mls). The solution was cooled in an ice bath and dry hydrogen chloride was passed for one hour. After standing in a refrigerator for three hours, the solution was evaporated down under vacuum and the residue was dissolved in pyridine. Dry hydrogen sulphide was bubbled through the solution for six hours. Chloroform was added to the solution and the pyridine was removed by extraction with dilute aqueous hydrochloric acid. The chloroform solution was washed, dried and the chloroform was distilled off under vacuum. The residue was chromatographed on a silica gel column (400 g). The main product was cholestanol thionoacetate (4.61 g) which recrystallised from chloroform/methanol to give colourless flakes, m.p. 91.5-93°, $[\alpha]_D \sim 0$, λ max 245 mμ (ε = 12,400); 368 mμ (ε = 27.5): N.M.R. spectrum: δ 5.3 (1H)(multiplet) ($CH_3CSO-\underset{|}{C}-\underline{H}$); δ2.5 (3H)(singlet)($\underline{CH_3}CSOCH$); δ 2.2-0.7 (46H)(overlapping multiplets). (Found: C, 77.8; H, 11.0; S, 7.2 $C_{29}H_{50}OS$ requires C, 78.0; H, 11.3; S, 7.2).

Synthesis of Cyclohexyl Thionoacetate

Cyclohexyl Thionoacetate was prepared as above from cyclohexanol (5.0 g) and acetonitrile (100 ml) and purified by chromatography on silica gel. Those fractions containing only cyclohexyl thionoacetate were combined and the solvents were removed by distillation under vacuum. The yellow liquid remaining was vacuum distilled, the fraction with b.p. = 121 - 123° (15 m.m.) being collected. Cyclohexyl thionoacetate (6.15 g; 77%) was obtained, ν max. 2945, 1550, 1460, 1305, 1260, 1210, 1190, 1125, 1105, 725, 700 cm^{-1}. (Found: C, 61.0; H, 8.9; S, 20.1. $C_8H_{14}OS$ requires C, 60.7; H, 8.9; S, 20.2)

Synthesis of Cyclohexyl Acetate

Cyclohexyl acetate was prepared by the method described by Vogel.[22] Dry hydrogen chloride was passed through cyclohexanol (40 ml) until the solution was saturated (1.5 hours). Glacial acetic acid (70 g) was added and the mixture was refluxed for 16 hours. The solution was then poured into water and the organic layer was washed with water, saturated aqueous sodium bicarbonate solution (4 times) and water again. The solution was dried over anhydrous calcium chloride, then distilled. The fraction boiling at 171-174° was collected (24.4 g).

Preparation of Mercury Benzamide

Mercuric oxide (2.5 g) and benzamide (2.0 g) were refluxed in ethanol (25 ml) for 30 minutes and the solution was filtered hot. The colourless crystals which were deposited on cooling, were recrystallised from ethanol to give colourless crystals (0.74 g, m.p. 220-222°)(Lit[19] m.p. 222-223°)

Preparation of Raney Nickel[23]

Nickel-aluminium alloy (50 g) was dissolved in small portions with stirring in a cold 25% aqueous sodium hydroxide solution (300 ml). The solution was heated on a water bath for 8 hours. The excess solution decanted off and the suspension washed by decantation with 10% aqueous sodium hydroxide solution, distilled water (25 times) and absolute alcohol (6 times). The alcohol was removed by azeotropic distillation with benzene. The Raney nickel was deactivated by refluxing in acetone for 2 hours. The acetone was removed by azeotropic distillation with benzene and the Raney nickel was stored under dry benzene for six weeks before use.

Raney Nickel Desulphurisation of Cholestorol Thionoacetate

Deactivated Raney nickel (1 g) was added to a solution of cholestanol thionoacetate (100 mg) in anhydrous benzene (50 ml). The suspension was refluxed for six hours. The

Raney nickel was filtered off and the benzene was evaporated under vacuum from the filtrate. The residue was chromatographed on a silica gel column (10 g). Some fractions had to be rechromatographed to give complete separation of the products. The products were identified by thin layer chromatography and mixed melting points with authentic cholestanol derivatives.

Mercury Salt Desulphurisations of Cholestanol Thionoacetate

100 mg of cholestanol thionoacetate was dissolved in the appropriate solvent and a solution of the mercury salt in slight excess was added. When the reaction was complete, dry hydrogen sulphide was bubbled through the solution to precipitate the remaining mercury salts, and the insoluble products were filtered off. The filtrate was evaporated down or the solvent was extracted into aqueous solution from chloroform when this was possible. This method was used for the removal of pyridine which was extracted into hydrochloric acid, and was followed by drying and evaporation under vacuum of the chloroform layer. In all cases the residue was identified by thin layer chromatography, and was chromatographed on silica gel (10 g) if a mixture of products was formed.

Most of the desulphurisations were carried out in a 100 ml conical flask fitted with reflux condenser and

Bunsen valve and flushed with dry nitrogen. The mercuric chloride desulphurisation was carried out firstly under these conditions and also in a glass ampule. This ampule was made from a short length of 8 mm glass tubing with an internal volume twice that of the reaction solution. After being sealed, the tube was heated in a boiling water bath for 20 hours.

Desulphurisation of Cyclohexyl Thionoacetate

Mercuric acetate (30 mg) was dissolved in the minimum amount of solvent and added to a solution of cyclohexyl thionoacetate (20 mg) in the same solvent. After the reaction was complete, dry hydrogen sulphide was passed to precipitate any remaining mercuric acetate. The suspension was centrifuged and the supernatent liquid was separated into its components by gas chromatography. This method was amended to allow complete separation of the liquid products from the mercuric sulphide. The reaction was carried out in the removable arm A of the apparatus shown in figure 17 The solution of products in γ-picoline was then frozen in dry ice/acetone and the system evacuated by an oil pump. With the tap closed, arm B was cooled in the freezing mixture and arm A allowed to come slowly to room temperature. The volatile organic products evaporated from arm A and recondensed in arm B.

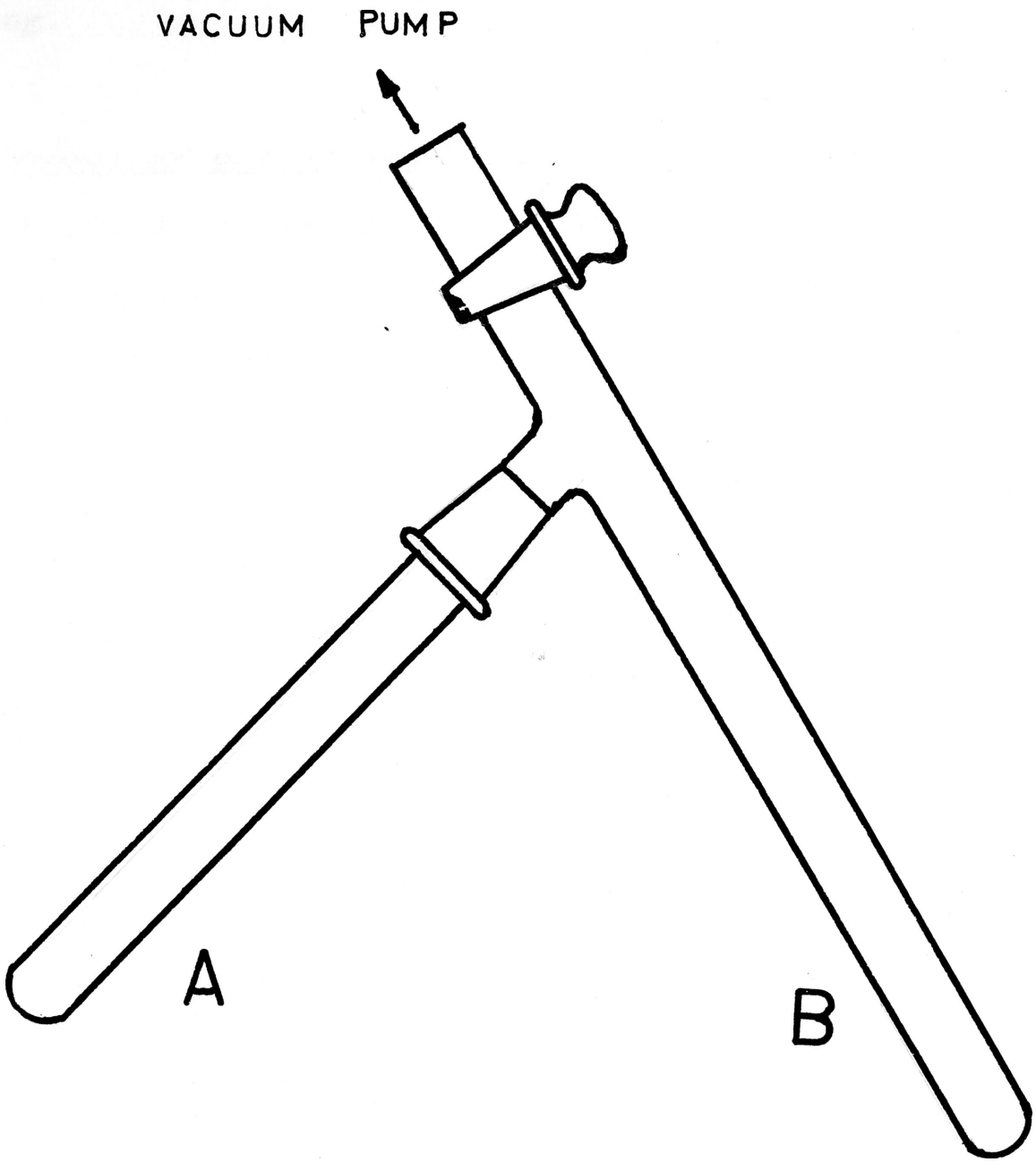


FIGURE 17

A slow temperature increase was necessary to prevent bumping.

Gas Chromatography of Desulphurisation Products

γ-picoline was chosen as the solvent for cyclohexyl thionoacetate desulphurisations since its retention time on the gas chromatograph was between those of acetic anhydride and cyclohexyl acetate. Pyridine was unsuitable since its peak obscured the acetic anhydride peak. The retention times at 155° and a flow rate of 5.0 cc/min. on a silicone column were: acetic anhydride, 3.0 minutes; γ-picoline, 4.7 minutes; cyclohexyl acetate, 7.8 minutes. Calibration charts were drawn up, relating peak area of the recorder to volume of acetic anhydride or cyclohexyl acetate injected. The relationship was linear over the range 0.4 - 1.0 (fig.18).

5 μl of the desulphurisation product mixture was injected into the chromatograph. The peaks were identified by injecting mixtures of the reaction products with authentic acetic anhydride and cyclohexyl acetate. From the peak areas (measured by approximation to triangles) and the calibration charts, the ratio of cyclohexyl acetate to acetic anhydride in the desulphurisation products was calculated.

Dimethylaniline was used as an internal standard to

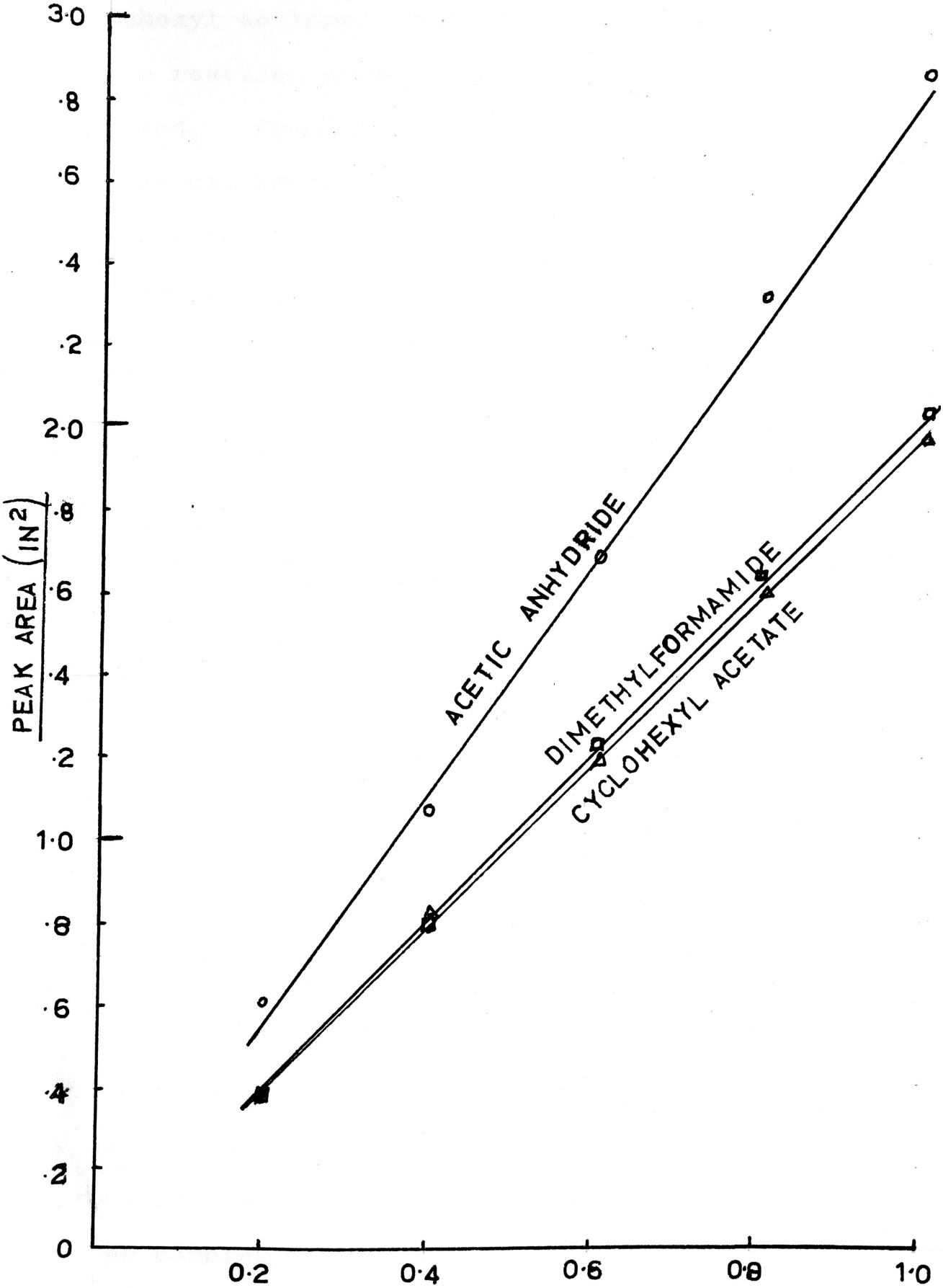

3·0
·8
·6
·4
·2
2·0
·8
·6
·4
·2
1·0
·8
·6
·4
·2
0
PEAK AREA (IN²)
0·2
0·4
0·6
0·8
1·0
VOLUME (µl)
ACETIC ANHYDRIDE
DIMETHYLFORMAMIDE
CYCLOHEXYL ACETATE

FIGURE 18

determine the absolute yield of acetic anhydride and cyclohexyl acetate. 30 μl of dimethylaneline was added to the reaction products and 5 μl of the mixture injected. From the area of the dimethaniline peak and the calibration chart for this compound (fig. 18) the fraction of the total 30 μl which was actually injected was calculated. This gives the fraction of acetic anhydride and cyclohexyl acetate injected. The amount of each product injected can be calculated from peak areas, hence the amount in the total product mixture can be calculated.

Analysis of Precipitate from Mercuric Chloride Desulphurisations

a) Mercury Analysis[24]

Approximately 100 mg samples of the precipitate were dissolved in aqua regia. The solution was diluted and the pH adjusted to 10-11 with ammonia. Potassium iodide (3 g) solution was added, then the solution was boiled. A hot aqueous solution of copper bisethylenediamine nitrate was added. Upon cooling to room temperature, violet crystals were formed and filtered in a sintered glass crucible. The crystals were washed four times with a dilute solution of potassium iodide and the copper complex, 3 times with ethanol and 3 times with anhydrous ether. After sucking dry for 10 minutes, the crystals were stored in a vacuum desiccator until

constant weight was attained.

b) Sulphur Analysis[25]

Approximately 100 mg of the precipitate was dissolved in aqua regia. The diluted solution was heated to boiling and a dilute boiling solution of barium chloride was added. After cooling the white precipitate of barium sulphate was taken off in a fine filter paper which was ignited at 600°C.

c) Chloride Analysis[26]

(i) The precipitate was boiled with sodium carbonate solution to bring the chloride into solution. The black precipitate was filtered off, then the solution was neutralised with nitric acid and buffered with ammonium acetate. The chloride was determined by *Mohr's* method, i.e. titration with standardised 0.1N silver nitrate using potassium chromate indicator. The results were found to be strongly pH and temperature dependent.

(ii) Gravimetric Method for Chloride

The chloride was brought into solution as before, but the solution was made slightly acidic and excess silver nitrate solution added. The suspension which was formed coagulated on heating. The solution was left to stand for 2 hours out of direct sunlight and was then filtered into a sintered glass crucible,

washed with 10^{-3}M nitric acid and dried for 30 minutes at 100° before weighing.

(iii) Volhard's method for Chloride

The chloride was brought into solution as before. The solution was made slightly acidic with nitric acid and then a known slight excess of 0.1N silver nitrate solution was added. Nitrobenzene (2 ml) was added with vigorous shaking to coagulate the precipitate. Ferric alum indicator was added and the solution was back titrated with 0.1N ammonium thiocyanate. The nitrobenzene is added to prevent the silver chloride precipitate from redissolving during the titration.

This analysis was repeated twice, bringing the chloride into solution by fusing the precipitate with a sodium carbonate/potassium carbonate fusion mixture.

d) Determination of Mercurous Chloride

The amount of mercurous chloride in the compound was determined by means of the following reaction:

$$Hg_2Cl_2 + I_2 + 6I^- \longrightarrow 2HgI_4^{2-} + 2Cl^-$$

100 mg of the precipitate was weighed out into a conical quickfit flask. Potassium iodide (1 g) and

standard iodine solution (10.00 ml) were added. The stoppered flask was shaken until all the compound had dissolved except for a small amount of yellow material. The solution was back titrated with standardised 0.1N sodium thiosulphate.

A C K N O W L E D G E M E N T S

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